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Hypereosinophilia after vaccination with the SARS-CoV-2 mRNA vaccines

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Clinical Implications

Hypereosinophilia may occur rarely after coronavirus disease 2019 vaccination and should be considered in patients presenting with symptoms consistent with eosinophilic disease. This may result from T_H2 skewing, a phenomenon observed in vaccine-associated enhanced disease, which has occurred with other vaccines.

One consequence of the coronavirus disease 2019 (COVID-19) pandemic has been widespread vaccination campaigns after the rapid development of the four vaccines now approved for use in the United States: the mRNA vaccines, Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273, the viral vector vaccine J&J/Janssen COVID-19 Ad26.COV2.S, and the protein subunit vaccine Novavax NVX-CoV237. Rare but significant side effects have been reported with these vaccines, including pericarditis and myocarditis with the mRNA vaccines and thrombosis and Guillain-Barré syndrome with the J&J/Janssen vaccine.[1] Laboratory surveillance during the clinical trials revealed a subset of patients with a transient decrease in blood lymphocyte count and increased C-reactive protein with the Pfizer vaccine and anemia and thrombocytopenia with the Moderna vaccine.[2,3] Peripheral eosinophilia after COVID-19 vaccination was not initially appreciated, but several case reports have since been reported with the Pfizer vaccine. These have been associated with clinical sequelae including non-episodic angioedema with eosinophilia, eosinophilic cellulitis, and a severe bullous eruption.[4-6] These patients presented with peripheral eosinophilia of 960 to 3,750 cells/μL occurring 3 days to 3 weeks after dose 2 of the vaccine. One case of organizing pneumonia occurred after dose 1 of the vaccine with the development of peripheral eosinophilia and worsening pneumonia after dose 2.[7]

Here, we report on the largest published case series to date of peripheral eosinophilia attributed to COVID-19 vaccination and the potential clinical consequences of eosinophilia in a cohort of patients who were vaccinated with either the Pfizer or Moderna vaccines.

The study was approved by the Institutional Review Board at National Jewish Health in Denver, Colo. An electronic medical records database search was performed to identify patients who received the Moderna, Pfizer, or J&J/Janssen COVID-19 vaccines from December 10, 2020 through July 24, 2021 and had an elevated absolute eosinophil count greater than 1,000 cells/μL (normal range, 0-400 cells/μL) after vaccination.

Included subjects had a recorded baseline eosinophil count less than 1,000 cells/μL before vaccination, received two doses of their respective mRNA vaccine, and had rising eosinophilia present on the first available laboratory values after dose 1 or 2 of the vaccine. Subjects were excluded if they had a history of eosinophilia greater than 1,000 cells/μL or an underlying medical condition associated with hypereosinophilia (not including allergic disease or malignancy with previously normal eosinophil count), or if they were receiving a medication with a high incidence of eosinophilia. Further analysis and a detailed case review were performed for all patients in whom eosinophilia was identified to evaluate the likelihood that eosinophilia resulted from vaccination versus other identifiable causes.

Of the 41,283 patients who were vaccinated during this period, 33,489 (~81%) had received Pfizer, 4,477 (~11%) received Moderna, and 3,368 (~8%) received the Janssen vaccine. Patient ages ranged from 12 to 102 years (mean age, 53 years). All patients demonstrating eosinophilia after vaccination had received either the Pfizer or Moderna mRNA vaccines. In total, we identified 16 cases (4.2 of 10,000 cases) of eosinophilia without another identifiable cause occurring after vaccination with one of the COVID-19 mRNA vaccines. Of these, 13 were associated with the Pfizer vaccine (81%) and three with the Moderna vaccine (19%). Table I lists clinical characteristics of these patients. Ten of these cases occurred in females (62%) and six in males (38%). Mean age of subjects was 64 years (range, 23-84 years). Table II details the course of eosinophilia in these patients. Eosinophilia greater than 1,000 cells/μL was first recognized at 76 and 53 days after doses 1 and 2 of the vaccine, respectively. There was a mean increase of 1200 cells/μL from baseline to peak eosinophil count. Three of the five subjects who had laboratory data between doses 1 and 2 experienced eosinophilia greater than 1,000 cells/μL after dose 1. In subjects who had available laboratory data and were not treated with corticosteroids or biologic therapy (n = 6), mean time to a decrease in eosinophilia less than 1,000 cells/μL was 103 days. One subject continued to have eosinophilia greater than 1,000 cells/μL at 306 days.

In nine of 16 patients (56%), eosinophilia was recognized by a medical provider. Seven (44%) presented with new or poorly controlled symptoms. Six (38%) had clinical presentations that prompted treatment with oral corticosteroids or anti-IL-5 biologics. Four of these patients had received the Pfizer vaccine and two had received Moderna. Five had an underlying diagnosis of asthma, in which three developed worsening respiratory symptoms, one developed worsening rhinitis and one had no significant change but had poorly controlled asthma at baseline. The presentations of two patients were attributed to possible allergic bronchopulmonary aspergillosis (they did not meet all criteria), and two to underlying asthma. A 23-year-old woman with a history of asthma was given the diagnosis of idiopathic hypereosinophilic syndrome after she experienced an eosinophil count of 4,300 cells/μL 1 week after receiving dose 2 of the Moderna vaccine. She was treated with mepolizumab after evidence of respiratory and cardiac involvement. Finally, one patient with a history of chronic cough but a negative initial asthma workup, was ultimately diagnosed with asthma after acute worsening of the cough and concurrent eosinophilia. The one patient who was not treated with oral corticosteroids or anti-IL-5 biologics had chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. This patient presented with

TABLE I. Characteristics of patients who developed eosinophilia 1,000 cells/μL or greater after vaccination with coronavirus disease 2019 mRNA vaccine (n = 16)

Characteristic	n (%)
Vaccine used	
Moderna	3 (19)
Pfizer	13 (81)
Demographics	
Mean age, y	64 (23-84)
Female	10 (62)
History of atopy*	8 (50)
History of asthma	7 (44)
Mean baseline eosinophil count, cells/μL	450 (200-800)
Baseline eosinophil count <500 cells/μL	8 (50)
Baseline eosinophil count >500 cells/μL and <1,000 cells/μL	8 (50)
Mean time between baseline eosinophil count and dose 1, d	283 (5-990)

Data are presented as n (% of subjects) except where otherwise specified. Other values are reported as mean value (range).
*Subjects had positive skin prick testing to environmental allergens, elevated total serum IgE, or a history of asthma and elevated FeNO.

TABLE II. Course of eosinophilia greater than 1,000/μL after coronavirus disease 2019 mRNA vaccination

Feature of eosinophilia	
Increase from baseline eosinophil count to peak eosinophilia, cells/μL	1200 (300-3700)
Time between dose 1 and initial eosinophilia, d	76 (5-224)
Time between dose 2 and initial eosinophilia, d	53 (−16 to 196)
Patients who developed eosinophilia between dose 1 and dose 2*	3/5 (60%)
Patients who developed clinical sequelae requiring treatment with oral corticosteroids or anti-IL-5 therapy	6/16 (38%)
Patients whose eosinophilia decreased to <1,000 cells/μL with subsequent laboratory values*	10/12 (83%)†
Patients whose eosinophilia decreased after treatment with oral corticosteroids or anti-IL-5 therapy*	4/10 (40%)‡
Patients whose eosinophilia decreased without treatment*	6/10 (60%)
Time from peak eosinophilia to decrease <1,000 cells/μL in patients not treated with oral corticosteroids or anti-IL-5 therapy, d	103 (48-213)

Data are presented as n (% of subjects) except where otherwise specified. Other values are reported as mean value (range).
*Includes patients where these laboratory data were available.
†Two patients remained elevated according to the most recent laboratory values at 51 and 306 days.
‡One patient had recurrence of eosinophilia after treatment with oral corticosteroids.

worsening dyspnea and fibrosis and was given nintedanib. No patients in the current cohort were given the diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome, and no specific skin findings were described. Liver function tests were performed in most of these patients and were found to be normal.

A possible explanation for the eosinophilia observed in these patients is a T_H2 skewing effect caused by the vaccine, akin to the proposed mechanism of the previously observed vaccine-associated enhanced disease. [8,9] This phenomenon has been noted in humans in vaccine trials for dengue virus, respiratory syncytial virus, and measles, as well as in animal models for other coronaviruses including SARS-CoV-1. These vaccines were found to promote immune responses that exacerbated disease after subsequent infection. Vaccine-associated enhanced disease has predominantly been reported to exacerbate respiratory disease; pulmonary eosinophilia is a characteristic feature.

Although COVID-19 infection after vaccination was confirmed in only one of the patients in this study who developed eosinophilia, information on symptomatic infection was not routinely collected for all patients, and many are known to develop asymptomatic infection. It is also possible that T_H2 responses seen with these vaccines were independent of post-vaccination infection and induced by vaccination alone. This theory is supported by the clinical consequences of eosinophilia predominantly being reported after dose 2 of the vaccine, after which more potent immunogenicity would be expected. It is also possible that the current population was more susceptible to a T_H2-skewed immune response, because many had confirmed features of atopy, including allergic asthma.

Our report confirms previous accounts of peripheral eosinophilia and eosinophilic disease occurring temporally after vaccination with the Pfizer COVID-19 mRNA vaccine. To our knowledge, we also report the first cases of this phenomenon occurring after vaccination with the Moderna vaccine. Although the occurrence of eosinophilia after COVID-19 vaccination appears to be rare, we are likely underestimating the prevalence, because most patients did not have blood drawn after vaccination and others may have presented to other institutions for follow-up. Thus, patients who have received one of these vaccines and present with symptoms that could be consistent with eosinophilic disease should be screened for peripheral eosinophilia.

Although we strongly support continued vaccination strategies to prevent severe illness owing to this virus, studies evaluating the long-term immunogenicity of these vaccines is warranted, because clinical trials were limited in their duration of follow-up and the size of cohorts. Subjects with underlying atopic or eosinophilic disease should be included in these studies, because they may be more prone to develop a T_H2-skewed response to the vaccines. Pending further study, we recommend a risk-benefit analysis be performed when considering additional vaccination in patients who developed unexplained eosinophilia after either dose of the mRNA COVID-19 vaccines, particularly when patients develop significant symptoms related to eosinophilia. If vaccination is deemed necessary, an alternative non-mRNA vaccine could be considered.

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